

Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendments to claims 26 and 90 may be found in the specification at page 23, lines 14-19, at pages 41-44, and throughout the Examples; support for the amendment to claim 93 may be found in the specification at pages 3-4, 10 and 39-40; and the amendment to claim 96 is sought to correct a typographical error in its dependency. Support for new claims 100-102 may also be found throughout the specification, particularly at pages 41-44 and throughout the Examples; support for new claims 103-105 may be found at pages 12, 15-16, 29 and 41-44, and in claim 28 as originally filed; support for new claims 106-108 may be found at pages 23, 36-38 and 41-45 of the specification; support for new claims 109-111 may be found at page 11, lines 24-26, at pages 41-44, and in claim 34 as originally filed; support for new claims 112-114 may be found at pages 12, 15-16, 29 and 41-44, and in claim 52 as originally filed; and support for new claims 115-117 may be found in the specification at pages 38-44. Hence, the foregoing amendments to the claims do not add new matter, and their entry into the present application is respectfully requested.

II. Status of the Claims

By the foregoing amendments, new claims 100-117 are sought to be entered, and claims 26, 90, 93 and 96 have been amended. These amendments do not add new matter.

Upon entry of the foregoing amendments, claims 26, 28-35, 52 and 89-117 are pending in the application, with claims 26 and 100-102 being the independent claims.

III. Summary of the Office Action

In the Office Action dated January 25, 2001, the Examiner has made one objection to, and five rejections of, the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

IV. The Objection to Claim 97

In the Office Action at page 3, the Examiner has objected to claim 97 as being dependent upon a rejected base claim, but has acknowledged the allowability of claim 97 if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants acknowledge this objection, and respectfully assert that in view of the amendments and remarks presented herein, claim 97 is allowable without further amendment. Hence, reconsideration and withdrawal of this objection are respectfully requested.

V. The Rejection Under 35 U.S.C. § 102(b) Over Bebee Is Traversed

In the Office Action at pages 3-6, the Examiner has maintained the rejection of claims 26, 28-35 and 52, and has newly rejected claims 89-93, 98 and 99, under 35 U.S.C. § 102(b) as being anticipated by Bebee. Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). By the foregoing amendments, claim 26 (and thus the remaining claims that ultimately depend therefrom) has been amended to indicate that at least one of the recombination sites used in the methods as presently claimed contains one or more mutations that enhance recombination specificity. In contrast, Bebee does not expressly or inherently disclose the use of engineered recombination sites (other than *lox* sites which are specifically excluded from the method of claim 26 as presently claimed) that comprise one or more mutations that enhance recombination specificity (or that remove stop codons, as in the method of new claim 100; that avoid hairpin formation, as in the method of new claim 101; or that comprise a sequence selected from SEQ ID NOs:1-16, as in the method of new claim 102). Bebee therefore does not expressly or inherently disclose every element of the invention as presently claimed.

In view of the foregoing remarks, and under *Kalman*, Applicants respectfully assert that Bebee cannot and does not anticipate the claims as currently presented. Reconsideration and withdrawal of the rejection of claims 26, 28-35, 52, 89-93, 98 and 99 under 35 U.S.C. § 102(b) over Bebee therefore are respectfully requested.

VI. The Rejection Under 35 U.S.C. § 102(e) Over Shuman Is Traversed

In the Office Action at pages 6-7, the Examiner has rejected claims 26, 28-35 and 52 under 35 U.S.C. § 102(e) as being anticipated by Shuman (U.S. Patent No. 5,766,891, Doc.

A1 cited on the Form PTO-892 attached to Paper No. 23; hereinafter "Shuman"). Applicants respectfully traverse this rejection.

As noted above, the claims as currently presented are drawn to methods in which at least one of the recombination sites used comprises one or more mutations that enhance recombination specificity, remove stop codons, avoid hairpin formation, or comprise a sequence selected from SEQ ID NOs:1-16. In contrast, Shuman does not expressly or inherently disclose the use of engineered recombination sites that comprise one or more such mutations. Shuman therefore does not expressly or inherently disclose every element of the invention as presently claimed.

In view of the foregoing remarks, Applicants respectfully assert that claims 26, 28-35 and 52 are not anticipated by Shuman. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) over Shuman are therefore respectfully requested.

VI. *The Rejection Under 35 U.S.C. § 103(a) Over Bebee In View of Hall Is Traversed*

In the Office Action at pages 7-9, the Examiner has rejected claims 26, 28-35, 52, 89-96, 98 and 99 under 35 U.S.C. § 103(a) as being unpatentable over Bebee in view of Hall *et al.*, *Molec. Microbiol.* 15:593-600 (1995) (Doc. "U1" on the Form PTO-892 attached to Paper No. 23; hereinafter "Hall"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one

of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). In the present case, this burden has not been satisfied.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Bebee and the deficiencies therein. Bebee is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness, as it does not disclose, suggest or otherwise contemplate recombinational cloning methods using recombination sites that comprise one or more mutations that enhance recombination specificity, remove stop codons, avoid hairpin formation, or comprise a sequence selected from SEQ ID NOs:1-16.

These deficiencies in Bebee are not cured by the disclosure of Hall, which also does not disclose, suggest or otherwise contemplate recombination sites comprising the above-described mutations. Indeed, Hall provides no disclosure or suggestion that one of ordinary skill should (or even *could*) modify the recombination sites disclosed in Bebee in order to obtain the enhanced recombination specificity of the methods of present claim 26. Hence, Bebee and Hall, alone or in combination, do not disclose or suggest the invention as presently claimed. The skilled artisan therefore would not have been motivated to combine the disclosures of these references in order to make and use the claimed invention. Absent such suggestion and motivation, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). Thus, the burden required to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 26, 28-35, 52, 89-96, 98 and 99 are not rendered obvious by the disclosures of Bebee and Hall, alone or

in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

VII. *The Rejection Under 35 U.S.C. § 103(a) Over Kilby or Snaith in view of Ausubel, Padgett, Grose, Hall and Baum Is Traversed*

In the Office Action at pages 9-15, the Examiner has rejected claims 26, 28-35, 52, 89-96, 98 and 99 under 35 U.S.C. § 103(a) as being unpatentable over Kilby *et al.* (Doc. No. AT10, of record; hereinafter "Kilby") or Snaith *et al.* (Doc. No. AR21, of record; hereinafter "Snaith"), in view of Ausubel *et al.* (Doc. "W1" listed on the Form PTO-892 attached to Paper No. 8; hereinafter "Ausubel") and further in view of Padgett *et al.* (Doc. "X1" listed on the Form PTO-892 attached to Paper No. 8; hereinafter "Padgett") or Grose *et al.* (Doc. "C1" listed on the Form PTO-892 attached to Paper No. 8; hereinafter "Grose"), Hall and Baum. Applicants respectfully traverse this rejection.

As noted above, the present claims are drawn to recombinational cloning methods using recombination sites that comprise one or more mutations that enhance recombination specificity, remove stop codons, avoid hairpin formation, or comprise a sequence selected from SEQ ID NOs:1-16. In contrast, none of the cited references, alone or in combination, discloses, suggests or otherwise contemplates the presently claimed methods. Therefore, one of ordinary skill would have found absolutely no motivation to have combined the disclosures of these references (and indeed, even if such a combination were proper, the combined disclosures of the cited references would not have resulted in the invention as presently claimed).

Moreover, in citing several passages from Applicants' own disclosure in analogizing "recognition sequences" and "recombination sites" (*see* Office Action at page 12, first paragraph; and at page 15, lines 2-4), the Examiner appears, at least in part, to be using the present disclosure as a template by which selected portions of the cited art may be pieced together in the attempt to support a *prima facie* case of obviousness of the presently claimed invention. Applicants wish to remind the Examiner, however, that this type of hindsight analysis is legally impermissible. As the Federal Circuit has held numerous times, the Examiner must instead show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure.").

The Board has also provided the same mandate on this issue:

it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . a rejection based on § 103 must rest on a

factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the language in Applicants' disclosure regarding the definitions of "recognition sequences" and "recombination sites" is irrelevant to the patentability of the invention as presently claimed, since it could only be used to support a hindsight obviousness analysis which is legally impermissible.

Hence, the cited references do not disclose or suggest the invention as presently claimed. The skilled artisan therefore would not have been motivated to combine the disclosures of these references in order to make and use the claimed invention. Accordingly, under *Fine*, these references may not be properly combined and a *prima facie* case of obviousness has not been established.

In view of the foregoing remarks, Applicants respectfully assert that claims 26, 28-35, 52, 89-96, 98 and 99 are not rendered obvious by the disclosures of Kilby or Snaith in view of Ausubel, Padgett, Grose, Hall and Baum, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

VIII. *The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Accommodated*

In the Office Action at pages 15-16, the Examiner has rejected claims 90, 93, 94 and 96 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse this rejection.

A. *The Recitations in Claim 90*

In making this rejection, the Examiner first contends that the distinction between the recitations "mutants," "variants" and "derivatives" in claim 90 is not clear, and that use of the plural forms of these terms in claim 90 further render the claim unclear as it allegedly is not clear which mutants, variants and derivatives are encompassed by this claim. Applicants respectfully disagree with these contentions. As one of ordinary skill would readily understand, although the distinctions between "mutants," "variants" and "derivatives" of a given molecule may be subtle, they are nonetheless significant. However, to expedite prosecution of the present application, by the foregoing amendments claim 90 has been amended to delete the recitations "mutants," "variants" and "derivatives."

In view of the foregoing remarks, Applicants respectfully assert that the foregoing amendments to claim 90 have fully accommodated this portion of the rejection. Reconsideration and withdrawal are therefore respectfully requested.

B. *The Recombination Sites in Claims 93 and 94*

The Examiner next contends that in claims 93 and 94, it is unclear whether the recombination sites recited in these claims are meant to be comprising the entire transposon

or transposable element or only those portions containing the transposase recognition site(s). By the foregoing amendments, claim 93 has been amended to recite the use of "transposase recognition sites of one or more transposons or transposable genetic elements." Applicants respectfully disagree with the Examiner's cautionary note (*see* Office Action at page 16, third paragraph, lines 3-4) that if claim 93 is intended to encompass the use of portions of transposons or transposable genetic elements that comprise the transposase recognition sequences, "then issues under enablement could be raised." *Id.* As noted above, the amendment to claim 93 is fully supported in the present specification, particularly at pages 3-4, 10 and 39-40. Moreover, as is specifically pointed out in the specification, the preference for particular recognition sites by certain transposases was well-known in the art at the time of filing of the present specification:

The recombinases of some transposons, such as those of conjugative transposons (e.g., Tn916) (Scott and Churchward, 1995. *Ann Rev Microbiol* 49:367; Taylor and Churchward, 1997. *J Bacteriol* 179:1837) belong to the integrase family of recombinases and in some cases show strong preferences for specific integration sites (Ike et al 1992. *J Bacteriol* 174:1801; Trieu-Cuot et al, 1993. *Mol. Microbiol* 8:179).

* * * *

An unrelated family of recombinases, the transposases, have also been used to transfer genetic information between replicons. Transposons are structurally variable, being described as simple or compound, but typically encode the recombinase gene flanked by DNA sequences organized in inverted orientations. Integration of transposons can be random or highly specific. Representatives such as Tn7, which are highly site-specific, have been applied to the efficient movement of DNA segments between replicons (Lucklow et al. 1993. *J. Virol* 67:4566-4579).

Specification at page 39, lines 13-18, and at page 40, lines 6-13. In order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. See *In re Howarth*, 210 USPQ 689, 692, (CCPA 1981). As noted above, the sources, locations, and DNA sequences of a variety of transposons or transposable genetic elements, and their interactions with corresponding transposases, were well-known in the art at the time the present application was filed. As also noted above, the present specification teaches methods of using transposons or transposable genetic elements, and their corresponding transposases, in the methods of the invention as presently claimed. Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the method of claim 93 as amended with a reasonable expectation of success and without undue experimentation. The present specification therefore fully enables claim 93 as currently presented.

Hence, Applicants respectfully assert that one of ordinary skill reading claims 93 and 94 in the context of the present specification and information that was readily available in the art, would readily understand the metes and bounds of the recitations contained in claims 93

and 94 as currently presented. Moreover, Applicants respectfully assert that the foregoing amendment to claim 93 does not raise issues of enablement, since claim 93 as currently presented is fully enabled by the present specification in view of information that was readily available to the ordinarily skilled artisan. Reconsideration and withdrawal of this portion of the rejection under 35 U.S.C. § 112, second paragraph, therefore are respectfully requested.

C. The Dependency of Claim 96

Finally, the Examiner notes that claim 96 depends from itself and therefore is unclear. Applicants apologize for this oversight, and thank the Examiner for the opportunity to correct this typographical error. By the foregoing remarks, the dependency of claim 96 has been amended such that this claim properly depends from claim 95. Thus, this portion of the rejection has been accommodated; reconsideration and withdrawal are therefore respectfully requested.

D. Summary

In view of the foregoing remarks, Applicants respectfully assert that claims 90, 93, 94 and 96 as currently presented particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

IX. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Date: July 25, 2001

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Version with markings to show changes made

In the Claims:

(a) Pending claims 26, 90, 93 and 96 are sought to be amended as follows:

26. (Four times amended) A method for synthesizing a double stranded nucleic acid molecule comprising

- (a) mixing one or more nucleic acid templates with a polypeptide having polymerase activity and one or more primers comprising at least a first recombination site or portions thereof;
- (b) incubating said mixture under conditions sufficient to synthesize a first nucleic acid molecule which is complementary to all or a portion of said templates and which comprises said first recombination site or portions thereof; and
- (c) incubating said first nucleic acid molecule in the presence of one or more primers comprising at least a second recombination site or portions thereof under conditions sufficient to synthesize a second nucleic acid molecule complementary to all or a portion to said first nucleic acid molecule, thereby producing a double stranded nucleic acid molecule comprising at least said first and second recombination sites or portions thereof, wherein at least one of said first and second recombination sites comprises one or more mutations that enhance recombination specificity, and wherein said first and second recombination sites are not *lox* sites.

90. (Once amended) The method of claim 89, wherein said Int recognition sites are selected from the group consisting of an *attB* site, an *attP* site, an *attL* site, an *attR* site, and [mutants, variants,] portions [and derivatives] thereof.

93. (Once amended) The method of claim 26, wherein said first or second recombination sites [are] comprise transposase recognition sites of one or more transposons or transposable genetic elements.

96. (Once amended) The method of claim [96,] 95, wherein said integrons are In2 integrons.

(b) New claims 100-117 are sought to be entered.